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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/436,184	11/08/1999	JACK R. WANDS	21486-032001US	6241

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
03/11/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	09/436,184	WANDS ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 27 February 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: _____.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

13. ☐ Other: _____.

/Karen A Canella/
Primary Examiner, Art Unit 1643

Continuation of 11. does NOT place the application in condition for allowance because: The reasons of record stated in the final action, namely, that the the specification is not enabling for the claims requiring the inhibition of tumor growth in a mammal, which reads on the treatment of a human patient with a naturally occurring tumor for the following reasons.

Anti-sense therapy requires uptake of the administered polynucleotide by the target tumor cells. The specification does not provide dosage or data for administering a therapeutically effective dosage of the complementary sequences of the regulatory regions of SEQ ID NO:3, or SEQ ID NO:3 itself, to tumor cells which would result in the inhibition of growth, reproduction or survival of cancer cells. It is noted that many anti-sense therapies which appear to be promising using transfection in vitro, fail to provide any therapeutic efficacy when administered in vivo. Dar and Huang (Molecular Pharmaceutics, 2006, Vol. 3, pp. 2805-2809) teach that antisense therapy is hindered by poor stability in physiological fluids and limited intracellular uptake (abstract). In an article published eight years after the year of the instant filing, Sundaram et al (Nucleic Acids Research, 2007, Vol. 35, pp. 4396-4408) teach that despite the conceptual simplicity of the antisense approach, utilization of antisense is impaired by poor cellular entry and rapid degradation (page 579, second column, first full paragraph). Thus it can be concluded from these references that the art is unreliable with respect to in vivo treatment.
Because of all the deficiencies discussed above, and the unreliability in the art, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the claimed invention.

Applicant has provided a Declaration under C.F.R. 1.132 to aver that mice transplanted with glioblastoma cells which were previously transfected with the instant anti-sense nucleic acid produced a substantially smaller tumor mass than mice transplanted with glioblastoma cells which were not transfected with the anti-sense construct. this has been considered but not found persuasive because it fails to overcome one of the major hurdles of antisense therapy with regard to tumor uptake as set forth above..

Applicant argues that the specification provides enough information to allow for the dosage and delivery of the nucleic acid in a pharmaceutically effective manner. This has been considered but not found persuasive for the reasons set forth in the rejection above, particularly in regard to the limited intracellular uptake in target tumors.

Applicant has provided the article by Patil et al to support the notion that anti-sense therapy is not an unpredictable art. This article has been considered but not found persuasive because the targeted tissue is the retina which not a tumor and thus issues of tumor uptake and breakdown of the administered nucleic acid by tumor proteases are not complicating factors. Further, Patil states "The innate ability of DNA-based drugs to be internalized by target cells is minimal under normal circumstances. In addition, poor biological stability and a short half-life result in unpredictable pharmacokinetics. furthermore, DNA molecules that do manage to enter the cell are subsequently subjected to intracellular degradation along with stringently restricted nuclear access". These statements serve to confirm the above rejection. Patil further states that over the past several years many improvements have been made in the DNA delivery systems. However, the instant specification must be enabled as of the filing date of November 8, 1999 and improvements in the art after that date cannot be construed as enabling the instant specification..

Applicants arguments have failed to overcome the above reasons of record.